Pathologic Fracture as Primary Presentation of Malignant Pheochromocytoma: A Case Report

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Abstract- Pheochromocytoma is a relatively rare tumor with no age preference. This tumor is usually diagnosed accidentally. Pathologic fracture as the primary presentation of malignant pheochromocytoma is an uncommon presentation. The present case is a 23 year old man with malignant pheochromocytoma that his first chief complaint was bone pain due to pathological fracture. The presence of bone lesions as the first manifestation of pheochromocytoma makes this case a quite unusual one.

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Keywords: Pheochromocytoma; Pathologic fracture; Initial presentation

Introduction

Pheochromocytoma is a relatively rare disease (1). Although it has no age preference, it usually occurs in the fourth and fifth decades. Pheochromocytoma is the endocrine tumor of the medial adrenal gland and sympathetic paraaortic glands (2). The latter group which is an extra-adrenal pheochromocytoma is called paraganglioma. Pheochromocytoma is extra-adrenal in 10% of cases, bilateral in 10%, is hereditary in 10%, and has malignant features in 5 to 10% (3). This disease is usually diagnosed incidentally during imaging investigations. This is partly due to its non-specific presenting signs and symptoms mimicking cardiovascular diseases and partly due to its indolent course with a usual three-year interval between the first presenting symptom and the diagnosis of the disease (1).

Due to catecholamine overproduction, these patients have three main classic symptoms consisting headache, sweating and palpitation. These symptoms do not differ between the malignant and benign tumors. These symptoms are similar to cardiovascular disorders especially hypertension (4).

The first step in diagnosis is the measurement of urine and serum catecholamines and metanephrines. Then the primary site of the tumor and possible metastases must be investigated through contrast-enhanced CT scan, Gadolinium-enhanced MRI, and PET scan. MIBG (metaiodobenzylguanidine) scan is a highly sensitive imaging study for this disease. Consequently, it should be included in imaging investigation of all suspected pheochromocytoma patients, especially the intra adrenal type (1,5).

Distant metastasis confirms the malignant nature of the disease. The malignant type of this disease is sometimes accompanied by autosomal dominant syndromes including neurofibromatosis type 1 (NF1) with its characteristic presentation (6,7). The primary treatment is surgical excision. Surgical excision subsides the signs and symptoms and declines catecholamine-induced complications. Although there is no definitive treatment for the malignant type of the disease, the excision of the primary lesion and surgical debulking of metastases may be helpful to alleviate symptoms (8).

Case Report

A 23-year-old man without familial and medical issue was referred to the orthopedic clinic because of limping and bone pain in his right thigh. The patient had been suffering from fever, sweating, weight loss and occasional morning nausea/vomiting, since 3-4 months ago. He had a rib fracture 3 months before admission. He was unable to walk at the time of physical examination.

Imaging investigations included pelvic CT scan that showed a small cyst in his right proximal femur and a

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hypodense lesion in acetabulum, and MRI which revealed an osteolytic lesion in the right iliac bone with extension to acetabular roof, mild joint effusion in hip joint, a heterogeneous lesion in the right femoral metaphysic and bone marrow invasion (Figure 1).

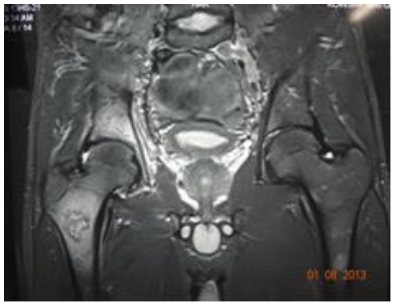

Figure 1. MRI of hip: revealed an osteolytic lesion in the right iliac bone with extension to acetabular roof, mild joint effusion in hip joint, a heterogeneous lesion in the right femoral metaphysic and bone marrow invasion

The patient underwent a bone biopsy with clinical diagnosis of simple cyst. The patient was referred to Oncology department with pathologic diagnosis of metastatic cancer with unknown source.

Abdominopelvic CT Scan showed multiple hypodense foci in the posterior right liver lobe and a large mass behind posterior liver lobe possibly having a retroperitoneal origin and destructive lesions in the right iliac wing and superior pubic ramus (Figure 2). In bone scan, increased uptake in the right sacroiliac joint, right acetabular roof and proximal femur, right frontal bone and right TMJ was found. Brain MRI showed an extra-axial mass in the right frontal lobe with concomitant involvement of the overlying skull bone. Plain pelvic X-ray showed osteopenia, disorganization, and deformity of the right femoral neck accompanied by severe osteoporosis in the right femoral neck and iliac wing as well as pathological fracture at the junction of right femoral neck to its shaft and cortical destruction.

Immunohistochemical (IHC) tests with CK, CK8/18, HMB 45, VMENTIN, EMA, CD117, LAC, S100 on the paraffin block of the metastatic femur was performed, which turned positive only for S100.

With diagnosis of metastatic cancer with unknown origin, the patient underwent chemotherapy with VAC regimen (vincristine, adriamycin, and cyclophosphamide) for three courses. In the second course of hospitalization, the patient's blood pressure was recorded up to 160/90. He had a 39-degree fever and became cyanotic with exertion on routine activities which improved after O2 therapy.

The sudden raised blood pressure was a valuable clue to the diagnosis of pheochromocytoma. The 24-hour urinary collection for creatinine, metanephrine, and normetanephrine were as follow: 24-hour urine volume was 1950cc, 24-hour metanephrine was 2659 (normal less than 350), and 24-hour normetanephrine was 7255 (normal less than 600). We prescribed Prasocine and Amlodipine. We requested IHC staining with NSE (neuron specific enolase) and CGN (chromogranin), both of which were positive. MIBG scan showed several foci of increased uptake including liver, thoracic spine, sacroiliac joints, pelvis and both femur (Figure 3). The final definite diagnosis was malignant pheochromocytoma.

Urology consultation was made in order to debulk the tumor. However, surgical excision was not performed due to patient's refusal. He underwent chemotherapy with Etoposide and Cisplatin.

The disease was unresponsive to chemotherapy. He became bedridden due to severe widespread bone pain and headache and vomiting. Bone scan showed multiple pelvic, proximal right femur, sternum and right shoulder. Brain MRI without contrast also showed right frontal bone lesion with pressure on the brain parenchyma and metastatic foci in posterior Sella-clivus. He was admitted for palliative radiotherapy with the protocol of 1200 rad in two fractions with one-week interval was applied for knee and right femur with cobalt 60 unit. He was discharged following partial subsiding bone pains.

He came back one week later with brain hemorrhage in brain metastasis possibly due to the hypertensive crisis and unfortunately finally passed away.

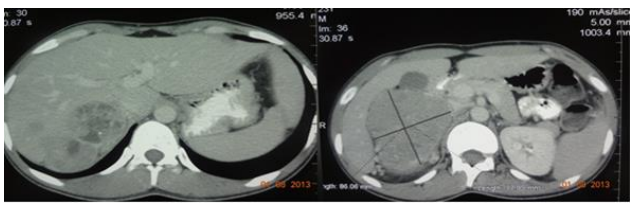

Figure 1. Abdominopelvic CTS at showed multiple hypodense foci in the posterior right liver lobe and destructive lesions in the right iliac wing and superior pubic ramus

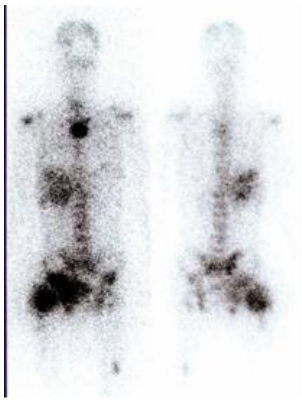

Figure 2. MIBG scan showed several foci of increased uptake including liver, thoracic spine, sacroiliac joints, pelvis and both femur

Discussion

Pheochromocytoma is a relatively rare tumor with an estimated incidence of 1 to 2 per 100,000 persons (1). This tumor usually occurs in the fourth and fifth decades of life. Pheochromocytoma usually is referred as the ten percent disease; it is bilateral in 10% of cases, occurs extra adrenal in 10% of cases and is malignant in 10% and is hereditary in 10% of cases (3).

Pheochromocytoma has three major presentations (headache, palpitation, and sweating). Other symptoms which mimic other diseases such as cardiovascular diseases include pallor, anxiety, nausea, fatigue, abdominal pain and even chest pain which are the results of catecholamine overproduction, and more commonly hypertension (1).

Diagnostic tools for this tumor include urine and plasma catecholamine measurements, abdominal CE-CT and MRI and PET. I131-MIBG is also used as a specific imaging tool for pheochromocytoma, especially the intra adrenal form. It is also used, in higher dose, as a pain relief method in metastatic patients (5).

Malignant form pheochromocytoma could be accompanied by autosomal dominant syndromes, especially MEN2, VHL, PGL4, PGL3, PGL1, NF1 (6, 7). Each of these syndromes has several specific signs and symptoms. The most common of these is NF1, and the least common is PGL3. However, Multiple neurofibromas, caféolated spots, axillary freckle, optic tract tumors and Iris hamartomas are among NF1 presentations (9).

Distant metastasis is the only definitive criterion for malignant pheochromocytoma. However, there are reports about the role of size and weight of the pheochromocytoma (10). It is defined whenever aberrant neuroendocrine tissue is present at the abnormal site. Neuroendocrine cells are typically found in the adrenal medulla, hypothalamus, pituitary gland and pulmonary epithelium.

Different studies have suggested various methods for differentiating between malignant and benign pheochromocytoma. These methods include evaluation the Ki67 level, tumor size, biochemical, histologic methods such as Adrenal gland Scaled Score and immunohistochemical measurements, the degree of necrosis, non-staining with S100, high level of chromogranin A, lower levels of urine catecholamine metabolites at the time of diagnosis, high blood pressure persisting after surgery and extra-adrenal location. However, the current consensus is that the only definitive criterion for malignancy is metastasis (11).

Nearly in 10% of patients with pheochromocytoma metastases develop. The most common site of metastasis is bone, and pathological fracture is a major cause of morbidity in patients with bone metastasis (12).

Present case highlights that metastatic pheochromocytoma should be included in the differential diagnoses of a patient presenting with the devastating recent onset of bone pain accompanied by hypertension and lytic bony erosions is imaging. It also shows that sometimes patient's pain could be very severe in the terminal stages and does not respond to any oncological treatment such as chemotherapy. Finally, the patient with bone metastasis might have other concomitant visceral metastases which might be lethal. Although our patient eventually passed away from intracranial hemorrhage following the hypertensive crisis, he was suffering debilitating bone pain until the last days of his life. Unfortunately, MBIG-I 131 was not available for palliative/ therapeutic purposes. It is now generally accepted that thorough blood pressure control is mandatory for long-term survival. Most patients with malignant pheochromocytoma succumb to the disease in a few years after the diagnosis.

Contributing factors to improve long-term survival in patients with malignant pheochromocytoma are: primary tumor resection after documenting malignancy, the absence of hypercatecholaminemia in spite of metastasis, proper blood pressure control and absence of metastasis in vital organs (13).

Unfortunately, our patient did not undergo surgery for the primary tumor, did not have a suitable blood pressure control, and had visceral metastases in critical organs such as liver and brain, which altogether made the prognosis worse for him finally leading to death.

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